Conclusions: 1) SCN5A+ pts have increased beat-to-beat repolarization variability. 2) WT provides insight into time and amplitude of T-wave variability without the need to identify T wave endpoints. 3) The combination of wavelet time and amplitude variability parameters provided very effective phenotypic identification of SCN5A+ pts.

11:00

843-3 Prevalence of the Bifid T Waves in Genotyped LQTS Children

L. Zhang, K.W. Timothy, J. Fox, M.H. Lehmann, K.J. Meyer, A.J. Moss, J.L. Robinson, P.J. Schwartz, M.T. Keating, J.A. Towbin, G.M. Vincent. *LDS Hospital, University of Utah, Salt Lake City, UT, USA*

Background: Our group previously reported that LQTS children had more bifid (obvious or subtle) T waves (BI-T) on 12-lead ECGs than normal children (NL). In this study we determined the frequency of BI-T by specific genotype in both younger and older children.

Methods: ECGs of 99 LQTS (58 LQT1, 26 LQT2, 15 LQT3), and 462 NL, all unmedicated, age range 0–15 yrs, were studied. Some patients had multiple ECGs at different ages, yielding 199 LQTS and 623 NL records for this study. The frequency of BI-T in 12 leads was compared for the three genotypes and NL in two age groups (0–5 yrs and 6–15 yrs) using Wilcoxon Matched-Pairs Signed-Ranks test.

Results:

	0–5 yrs				6–15 yrs			
	NL	LQT1	LQT2	LQT3	NL	LQT1	LQT2	LQT3
BI-T%*	18.5	45	63	2.1	8.6	14	64.8	4.8
p**		0.0022	0.0047	0.0076		0.0653†	0.0029	0.0995

* average of all 12 leads ** each genotype compared with NL † obvious plus subtle BI-T; for subtle BI-T alone, p = 0.0029

The frequencies of BI-T within genotypes were significantly different: LQT2 >LQT1 >LQT3 (p values not shown) in both age groups. In LQT1, the frequency of BI-T also varied by age, with a lower % in older children (p = 0.0022).

Conclusions: LQT1 and LQT2 children have significantly more BI-T than do NL. The frequency of BI-T in LQTS children is different by genotype with the highest in LQT2 and lowest in LQT3. The frequency decreases with increasing age in LQT1, whereas it remains unchanged in LQT2. These findings may increase understanding of LQTS genotype pathophysiology, and may be helpful for clinical diagnosis.

11:15

843-4 A Mutation in KVLQT1 Causes Decreased Sinus Rate Without Evidence of Autonomic Nervous Abnormalities

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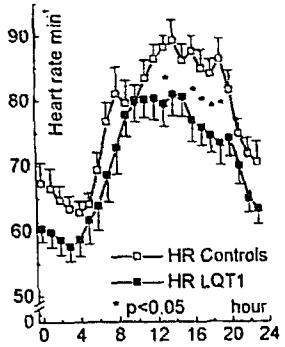
Background: We previously demonstrated abnormally low maximal heart rate during maximal exercise test in long QT syndrome type 1 (LQT1) patients. We therefore investigated whether a sinus node impairment is also present at lower heart rates and whether it is associated with altered autonomic nervous activity.

Methods: Circadian rhythmicity of heart rate (HR) and heart rate variation (HRV) were assessed in 19 LQT1 patients with Asp188Asn mutation of KVLQT1 gene (LQT1) and 19 healthy controls (C) matched for age (LQT1: 41 ± 19, C: 39 ± 19 years) and gender (7 men, 12 women in each group). All subjects underwent 24-hour Holter recording in sinus rhythm without medications.



	LQT1	C	p-value
HR	70 ± 10	76 ± 8	<0.05
SDANN	144 ± 45	136 ± 31	NS
HF	14 ± 7	16 ± 10	NS
LF	23 ± 10	27 ± 9	NS
LF/HF	1.7 ± 0.4	1.9 ± 0.5	NS

Results: HR was lower in LQT1 (table and fig.). No differences were found in HRV variables (table).

Conclusions: Sinus rate was found lower than normal even during rest and regular daily activities. The decreased rate could not be attributed to any alteration in autonomic nervous function. These results suggest that a potassium channel defect in KVLQT1 is responsible for the decreased sinus rate.

11:30

843-5 ECG Repolarization Parameters in LQTS Family Members With Borderline QTc Duration and Cardiac Events

W. Zareba, A.J. Moss, J. Robinson, M. Andrews, P.J. Schwartz, G.M. Vincent, S.G. Priori, J. Benhorin, E.H. Locati, J.A. Towbin, M.H. Lehmann, W.J. Hall, C. Napolitano, L. Zhang, K. Timothy. *University of Rochester, Rochester, NY, USA*

QTc duration of 0.42–0.47 sec can be found in both linked and non-linked LQTS pts. The aim of the study was to evaluate an association between clinical and ECG variables with cardiac events (CE) in 2,008 family members of LQTS pts with borderline QTc (0.42–0.47) enrolled in the International LQTS Regstry. Results of CE and noCE groups as follows:

Variables	no CE (n = 1,715)	CE (n = 293)	
Median Age at ECG (yrs)		28	29
Females		946 (55%)	197 (67%)*
Mean RR (ms)		787 ± 191	864 ± 212*
Age-adjusted bradycardia		267 (16%)	77 (26%)*
QTc (ms)		436 ± 18	446 ± 21*
QTmc (ms)		341 ± 27	353 ± 29*
TmTpc (ms)		95 ± 24	93 ± 23
L2 T wave: flat	112 (7%)	23 (8%)	
broad	40 (2%)	7 (2%)	
bifid biphasic	42 (2%)	7 (2%)	

* p < 0.001

Conclusions: In LQTS family members with borderline QTc duration, a longer QTc duration, bradycardia, and female gender are associated with increased likelihood of cardiac events. Morphologic T-wave abnormalities are infrequent and do not have prognostic significance in LQTS family members with borderline QTc.

11:45

843-6 Non-stationarity of Microvolt T Wave Alternans in Long QT Syndrome Patients

L. Burattini, W. Zareba, J.P. Couderc, J.A. Konecki, A.J. Moss. *University of Rochester, Rochester, NY, USA*

Background: Detection of microvolt T wave alternans (TWA) is a non-invasive method to identify pts at risk for sudden cardiac death. ECG tracings with visible TWA often show non-stationary pattern of this phenomenon. The purpose of the study was to evaluate stationarity of TWA in long QT syndrome (LQTS) pts, using our new correlation method (CM) for microvolt TWA detection.

Method and Results: Differently from accepted spectral method (SM), CM is able to identify TWA in as few as seven beats, and to detect which beats are alternating. In a group of 32 LQTS pts, 128-beat ECG recordings were performed to detect TWA using both CM and SM. TWA was identified by CM in 14 (44%) pts, and in 4 (13%) pts using SM. The features of TWA detected by CM in relation to the number of alternating beats (N) are shown in the following table (A_{CM} = alternans correlation amplitude; NS_TWA = non-stationary TWA; SNS_TWA = strongly NS_TWA; S_TWA = stationary TWA).

	SNS_TWA N < 38	NS_TWA 38 ≤ N ≤ 64	S_TWA N >64	p**
#pts	8	4	2	
N	20 ± 9	45 ± 10	78 ± 15	
A_{CM} (μV)	83 ± 51	35 ± 14*	44 ± 5*	0.094
RR (ms)	957 ± 203	1115 ± 55*	1264 ± 22	0.061

* p < 0.05 when comparing SNS_TWA vs. NS_TWA and S_TWA. ** Kruskall-Wallis Test

Significant correlations between A_{CM} and RR (r = 0.70; p = 0.005) and between N and RR (r = −0.57; p = 0.033) were observed.

Conclusions: 1) LQTS pts show non-stationary TWA more frequently than stationary TWA. Usually, 30-40 beats out of 128 were alternating. 2) Our correlative method was more effective than SM in non-stationary TWA detection. 3) Non-stationary TWA is associated with higher heart rate.

844 Serum Lipids and Hemostasis: Human Studies

Tuesday, March 31, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Room 255W

10:30

844-1 Treatment of Hypercholesterolemic Patients With and Without Coronary Disease With Pravastatin Decreases Thrombus Formation Under Dynamic Flow Conditions

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Background: Lowering cholesterol (C) decreases platelet reactivity in coronary disease (CAD) patients, but its effect on non-CAD patients has not been previously described.

Methods: We prospectively studied 40 stable patients with untreated LDL-C >145 mg/dl. CAD patients received Pravastatin (Prav), and non-CAD patients were randomized to Prav vs. Placebo (double-blind). All patients were on AHA step 1 diet. Thrombus formation was assessed blindly with a previously validated ex-vivo perfusion chamber system: non-anticoagulated blood was passed directly from the patient's vein over a standard substrate (porcine aortic media), under controlled rheologic conditions mimicking mild arterial stenosis (shear rate 1690s^{-1}). Perfusions were performed at baseline, 3, and 6 months. Specimens were stained with CME, and for fibrinogen. The cross-sectional thrombus area (TA, in $\mu m^2 \times 10^3$) was planimetered.

Results: Both Prav groups showed decreased LDL-C by 30% within 6 weeks (188 to 126 mg/dl, p < 0.001 vs baseline), and decreased TA (table). Placebo produced no changes in either LDL-C or TA. ΔLDL-C and ΔTA were modestly correlated (r = 0.49; p < 0.005).

	Baseline TA	3 month TA	6 month TA
Prav. +CAD (n = 16)	12.5 ± 2.1	10.9 ± 2.9*	10.5 ± 3.8**
Prav. −CAD (n = 12)	14.6 ± 3.4	11.6 ± 2.3**	10.4 ± 2.8**
Placebo, −CAD (n = 12)	12.2 ± 1.9	12.8 ± 2.7	13.2 ± 4.5

* p < 0.07, ** p < 0.04 vs. baseline. Values as mean ± SD

Conclusion: Prav therapy significantly decreased ex-vivo thrombus formation in high LDL-C patients, with and without CAD. This may, in part, explain the beneficial effects of Prav in primary as well as secondary prevention of CAD.

10:45

844-2 Lipid Lowering Therapy Reduces Blood Thrombogenicity in Hypercholesterolemic Patients: Effect of Simvastatin

U. Rauch, J.J. Badimon, D.A. Vorchheimer, I. Guzman, K. Harris, P. Harris, D.A. Sandler, J.T. Fallon, V. Fuster, J.H. Chesebro. *Cardiovascular Institute, Mount Sinai School of Medicine, New York, NY, USA*

Lipid reduction improves clinical outcome of CAD patients despite minor angiographic plaque regression. Normalization of endothelial function and plaque stabilization are two of the proposed mechanisms. We hypothesize that lipid reduction modulates blood thrombogenicity. Blood thrombogenicity was measured as thrombus formation (THR) in an ex vivo perfusion chamber. Hyperlipidemic patients (10 with and 5 without CAD) with total cholesterol (Cho) >220 mg/dl and LDL >140 mg/dl at baseline and after 3- months treatment with simvastatin (20 mg/day) were studied. Blood was perfused directly from the patient into the chamber at shear conditions typical of a mild coronary stenosis (1690/s) for 5 minute periods. Porcine aortic tunica media (model of severe arterial injury) served as the thrombogenic substrate. Thrombus formation was measured as area (μm^2/mm), analyzed by 2 independent blinded observers using computer-assisted planimetry.

Patients	baseline			3-months		
	Cho	LDL	Thrombus	Cho	LDL	Thrombus
CAD	253	189	10482	167*	106*	8605*
No-CAD	277	205	9988	183*	110*	7891*
All Pts	261	172	10317	194*	108*	8366*

* p < 0.05

Lipid reduction by simvastatin reduces blood thrombogenicity. It was previously suggested that this effect is exclusive to pravastatin. Our results indicate that the antithrombotic effect is mediated by lipid reduction and independent of the hypolipidemic agent used.

11:00

844-3 Elevation of Plasminogen Activator Inhibitor Type-1 (PAI-1) in Normal Subjects by Induction of Hyperinsulinemia With Hyperglycemia and Hypertriglyceridemia

J. Calles-Escandon, S. Mirza, B.E. Sobel, D.J. Schneider. *University of Vermont, Burlington, VT, USA*

Hypofibrinolysis caused by increased PAI-1 has been implicated in the vasculopathy of type 2 diabetes, typified by increased insulin, glucose and triglycerides. However, short term infusions of insulin have not increased PAI-1 in normal subjects. We hypothesized that induction of increased insulin accompanied by increased glucose and triglycerides would increase PAI-1. Accordingly 30% glucose and 10% Intralipid were infused for 6 hours in 10 normal lean individuals (54 ± 3 y) resulting in increased insulin (42 ± 5 μU/dL), glucose (200 ± 24 mg/dl) and triglycerides (425 ± 45 mg/dl) simulating changes in type 2 diabetes.

Results: In contrast to results with infusion of saline alone (n = 16) and euglycemic hyperinsulinemic clamps (n = 10, serum insulin = 89 ± 7 μU/dL), PAI-1 in blood increased significantly 6 hr after the onset of infusion (15 ± 5 ng/ml, p < 0.05 vs baseline = 7.4 ± 1.1, saline 6 hr = 3.4 ± 1.1 and insulin at 6 hr = 3.7 ± 0.8) and remained elevated for an additional 6 hr (combined infusion = 13.8 ± 3.8 ng/ml, saline = 6.7 ± 2 ng/ml, insulin alone = 7.8 ± 1.7 ng/ml, p = 0.06).

Conclusions: Our data suggest that combined hyperinsulinemia, hypertriglyceridemia and hyperglycemia are likely to contribute to hypofibrinolysis of type 2 diabetes by increasing the blood levels of PAI-1. Moreover, these results underscore the potential importance of modifying insulin resistance as well as achieving glycemic and lipidemic control in individuals with type 2 diabetes.

11:15

844-4 Beneficial Effect of Estrogen Therapy on Fibrinolysis Is Independent of Changes in Low-Density Lipoprotein Levels

K.K. Koh, M.N. Bui, L. Hathaway, R.O. Cannon III. *NHLBI, NIH, Bethesda, MD, USA*

We have previously shown that oral conjugated equine estrogen (CEE) reduces plasminogen activator inhibitor (PAI-1) levels in postmenopausal women, an effect associated with proportionate increases in degradation products of fibrin. However, oral estrogen reduces low-density lipoprotein cholesterol (LDL-C) levels that may account for PAI-1 effects, as oxidized LDL stimulates endothelial synthesis of PAI-1 in cell culture experiments. To assess the importance of LDL on PAI-1, we administered CEE 0.625 mg, simvastatin 10 mg, or the combination daily for 6 weeks each to 25 hypercholesterolemic (LDL = 165 ± 37 mg/dL; mean ± SD) postmenopausal women in a randomized, double-blind, double-crossover study. Data = % change from respective pretreatment values.

	CEE	Simvastatin	CEE/Simvastatin
LDL-C	-1* ± 11*	-24 ± 14**	-33 ± 13**
ApoB	-8 ± 8*	-23 ± 10**	-28 ± 11**
PAI-1	22 ± 47**	+27 ± 85	-23 ± 42***

*P < 0.001, **P < 0.005, ***P < 0.02 vs. respective pretreatment baseline values. † P < 0.005 vs. CEE

Only therapy including CEE reduced PAI-1 antigen levels, despite a greater effect of simvastatin on reduction in LDL-C and apolipoprotein B levels. Further, there was no synergism of combined CEE and simvastatin therapy on PAI-1 levels. These data suggest that estrogen reduces PAI-1 levels independent of changes in LDL. This primary effect of CEE on fibrinolytic potential may favor its use in hypercholesterolemic postmenopausal women, even if they are already on lipid-lowering therapy.

11:30

844-5 Low-Dose Estrogen Improves Serum Lipids, Homocysteine, and Fibrinolysis Without Altering Markers of Hemostasis in Elderly Men

S. Giri, P.D. Thompson, J.H. Contois, P. Taxel, J. Otvos, R. Allen, G. Ens, A.H.B. Wu, D.D. Waters. *Hartford Hospital, University of Connecticut, Hartford, CT, USA*

The effect of estrogen on cardiovascular risk factors in men is not well defined.